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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Subject: EPA ID # 007969-00053. 6(a)(2) Data on the Effects of Vinclozolin on a Second Interim Report on a Chronic Feeding Study (MRID# 423551-01, and -02)/Preliminary 90-Day Study with 1-Month and 3-Months recovery (MRID# 423551-03)/90-Day Study with 2-Months Recovery in Rats (MRID# 423551-04) and Literature Submissions (No MRID#).

Shaughnessy No.: 113201.
Tox. Chem. No.: 323C.
DP Barcode: D179889.
Case: 037677.
Submission No.: S420450.
Action: 405 6(a)(2) adverse data.

From: David G Anderson, PhD. David G Anderson 12/9/92
Section 3, Toxicology Branch-I
Health Effects Division (H7509C)

To: Susan Lewis/Robert Rose PM 21
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Registration Division (H7505C)

Thru: Karen Hamernik, PhD.
Acting Section Head, Section 3 K. Hamernik 12/9/92 KB 12/14/92
Toxicology Branch-I
Health Effects Division (H7509C).

CONCLUSIONS: This 6(a)(2) report of a chronic study in rats is the second interim report. When the final report is submitted, a detailed Data Evaluation Record (DER) will be prepared.

Although this second interim report on the chronic study does not change the current RfD, it adds histological support to the adverse gross tumor data, submitted previously (Reviewed by W. Greear in HED Doc.# 008311) as 6(a)(2) data on the same chronic study.

The other data submitted for this action, presented evidence that the Leydig cell tumors seen resulted from the antiandrogenicity of vinclozolin. The data suggest that in the absence of a hormonal imbalance, the tumors would fail to develop and that the vinclozolin induced tumors were a threshold effect with little relevance to human Leydig cell tumors.

The following study reports were submitted as 6(a)(2) data and reviewed:

1. Data on the Effects of Vinclozolin on a Second Interim Report on a Chronic Feeding Study (MRID# 423551-01, and -02),

Recycled/Recyclable

2. Preliminary 90-Day Study with 1-Month and 3-Months recovery (MRID# 423551-03),
3. 90-Day Study with 2-Months Recovery in Rats (MRID# 423551-04), and
4. Three Literature Submissions (No MRID#).

REQUESTED ACTION:

RD requested a review of data submitted under 6(a)(2) from BASF through Rodney Akers,

Second Interim Report; Study of the Chronic Toxicity of Reg. No. 83 258 (Vinclozolin) in Wistar Rats; Adminstration Via the Diet over 24 Months, Project 71S0375/88026 Including Preliminary Information of Two Reversibility Studies. Reg. Doc. No. BASF 92/10470. MRID# 423551-01.

Draft Pathology Report; Study of the Chronic Toxicity of Reg. No. 83 258 (Vinclozolin) in Wistar Rats; Adminstration Via the Diet over 24 Months, Project 71S0375/88026. 92/10547. MRID# 423551-02.

Preliminary Information of Selected Findings of Reversibility Study I of Reg. No. 83 258 (Vinclozolin) in Wistar Rats; Dietary Administration for 3-Months and 1-Month and 3-Months Recovery Period. Project No.: 39S0375/88116. 92/10548. MRID# 423551-03.

Preliminary Information of Selected Findings of Reversibility Study II of Reg. No. 83 258 (Vinclozolin) in Wistar Rats; Dietary Administration for 3-Months and 8-Week Recovery Period. Project No.: 99S0375/88114. 92/10549. MRID# 423551-04.

A Compilation of Published Documents Referenced in BASF Corporation Registration Document No.: 92/10470. BASF Reg. Doc. No. 92/5080. No MRID#.

(1) SA Roberts, TM Nett, HA Hartman, TE Adams and RE Stoll. SDZ 200-110 Induces Leydig Cell Tumors By Increasing Gonadotropins in Rats. J. Am. Col. Toxicol. 8: (#3) 487-504 (1989).

(2) F Neumann. Early Indicator for Carcinogenesis in Sex-Hormone-Sensitive Organs. Mutation Res. 248: 341-356 (1991).

(3) M Pavone-Macaluso, V Serretta, G Daricello, C Pavone, M Cacciatore, C Romano and N Caballo. Is There a Role for Pure Antiandrogens in the Treatment of Advanced Prostatic Cancer? Uro-Oncology: Current Trends, pages 149-157 (1990).

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BASES FOR THE CONCLUSIONS:

MRID# 423551-01 and -02:

These submissions on the chronic feeding study in rats (83-1) are interim reports. Selected histology was conducted for the study to more rapidly report on the gross tumor data noted at necropsy and reviewed in HED Doc.# 008311. The tumor incidence data may change with a larger number of treated animals and a more complete histological examination.

Doses administered were 0, 150, 500, 1500, and 4500 ppm (Approximately 0, 7.5, 25, 75, or 225 mg/kg/day) of vinclozolin in the feed to 20 Wistar rats/sex/group for 24-months.

Non-neoplastic results:

NOEL: < 150 ppm.

LEL: < 150 ppm for lenticular degeneration of the eye and vacuolation of pancreatic acinar cells in males and females. In males, testicular tubular calcification, slight interstitial cell fibrosis of the prostate gland, prostate and epididymal atrophy, and epididymal azoospermia and/or oligospermia occurred. In females, lipidosis of ovarian interstitial cells and ovarian stromal hyperplasia occurred. At 500 ppm in males, reduced prostatic secretions, adrenal cortical lipidosis and pituitary diffuse hyperplasia occurred. At 1500 ppm in males and females, cellular hypertrophy, and single cell necrosis were noted. In addition, males at the same dose level demonstrated eosinophilic foci of the liver, cystic rete testis, atrophic coagulating gland and pigment deposition in the ganglion. At 4500 ppm in males, focal necrosis of the liver, calcification of the kidney pelvis, epididymal granuloma, splenic hematopoiesis and adrenal focal hyperplasia occurred.

The body weight of males was 67% of control values and that of females was 70% of control values in the 4500 ppm dose group at the end of 24-months. Survival in males was 55%, 60%, 70%, 70% and 60%, respectively in controls, 150, 500, 1500 and 4500 ppm dose levels at 24 months. Survival in females was 85%, 80%, 75%, 85% and 60%, in the same repective groups at 24 months. The decreased survival in females at 24 months may have been biologically significant.

The registrant has argued that the 13% and 33% body weight reduction at 1500 and 4500 ppm in males indicates that the MTD was exceeded. It is noted that in males and females, cellular hyperplasia and single cell necrosis of the liver was elevated at 1500 ppm and above. However, survival was not reduced in males, but may have been reduced in females at the 4500 ppm. Whether or not dose levels necessary to determine carcinogneicity were exceeded must wait for the review of the final report on the study.

Neoplastic lesions:

Neoplastic lesions were demonstrated by increased incidence of benign testicular Leydig cell tumors at 150 ppm and higher and hepatocellular carcinoma in 1 male at each of the 500 and 1500 ppm dose levels. At 4500 ppm 9/20 males exhibited

hepatocellular carcinoma. Two male rats had malignant Leydig cell tumors, 1 at 1500 ppm and 1 at 4500 ppm. An increasing trend in males occurred for malignant neoplasms of all types. No dose relationship appeared to occur in neoplastic lesions in females sacrificed at term. An increasing trend appeared to occur in females sacrificed moribund or dying before termination, but it may not be real. A slight increased trend may have occurred when these two groups were added and malignant tumors were considered in all female animals, but the dose relationship is poor.

A dose related increase occurred in bilateral adrenal cortical nodules in males and females at 500 ppm and above. The report did not make it clear that these nodules were neoplastic. This should be clarified in the final report.

If the neoplastic lesions observed in this study occurred because of the antiandrogenic properties of vinclozolin, then vinclozolin should be regulated on the bases of a threshold for induction of hormonal perturbation.

Core classification: Supplementary because the rep : is an interim report and there is no NOEL as required by the guidelines.

MRID# 423551-03:

This is a preliminary report on a 90-day subchronic feeding study in rats (82-1) with 1-month and 3-months recovery undosed. Results from gross necropsy on selected target organs and selected target organ weights were recorded.

Doses administered were 0, 1000 and 4500 ppm (Approximately 0, 50, or 225 mg/kg/day) of vinclozolin in the feed to 30 Wistar rats/sex/group for 90-days with 1-month and 3-months recovery undosed.

NOEL: < 1000 ppm, but a NOEL (determination) was not intended.

LEL: < 1000 ppm (50 mg/kg/day) (LDT) for a increased liver, testes, pituitary and adrenal weights and decreased epididymal and kidney weights in males. Increased liver, ovary and adrenal weights occurred in females after 3-months dosing. After 3-months recovery undosed, in the 1000 ppm group, prostate weights were decreased in males and adrenal weights were decreased in females. At 4500 ppm and 3-months dosing in males, increased liver, testes, adrenal and pituitary weights and decreased epididymal, seminal vesicles and prostate weights in males were noted; in females increased liver, adrenal and pituitary weights and decreased uterine weights occurred. After 3-months recovery undosed, males in the 4500 ppm group showed decreased prostate and kidney weights; females showed increased spleen and liver weights and decreased adrenal weights.

Core classification: Supplementary because the report is an preliminary report on a special study not required.

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MRID# 423551-04:

For this preliminary report on a 90-day subchronic feeding study in rats (82-1) with 2-months recovery, plasma endocrine levels in males and females were analyzed for LH, FSH, ACTH, testosterone, estradiol (E2), corticosterone, aldosterone (Aldo), dehydroepiandrosterone (DEHA).

Doses administered were 0 and 4500 ppm (Approximately 0 or 225 mg/kg/day) of vinclozolin in the feed to 20 Wistar rats/sex/group for 90-days with 2-months recovery undosed.

NOEL: < 4500 ppm, but a NOEL was not intended.

LEL: < 4500 ppm (approximately 225 mg/kg/day) for elevated levels of ACTH, LH, FSH, testosterone, corticosterone, aldosterone and dehydroepiandrosterone in males. Estradiol in males may have been slightly depressed compared with control values. In females, ACTH and LH levels were elevated after the 3-months of dosing. Corticosterone and aldosterone levels were depressed compared with controls in females. These latter data are inconsistent with the elevated levels of ACTH. Controls were comparable with FSH, testosterone, dehydroepiandrosterone and estradiol levels in dosed females.

After 2-months recovery all male hormone levels were normal, except, FSH may have been slightly elevated. After 2-months recovery all female hormone levels were normal, except, estradiol may have been slightly elevated.

Core classification: Supplementary because the report is an preliminary report on a special study not required.

Summary of submitted literature:

Three references were submitted with the interim report on the chronic studies, which support the registrants belief that the Leydig cell tumors induced by vinclozolin are due to the antiandrogenic nature of vinclozolin (A compilation of Published Documents Referenced in BASF Corp. Registration Document No. 92/10470, MRID# 423551-01).

(1) One of these published papers,
[SA Roberts, TM Nett, HA Hartman, TE Adams and RE Stoll. SDZ 200-110 Induces Leydig Cell Tumors By Increasing Gonadotropins in Rats. J. Am. Col. Toxicol. 8: (#3) 487-504 (1989)]
presents data indicating elevated levels of LH from SDZ-200-110 treatment induces Leydig cell tumors in rats. Certain differences in the response between rats and humans (SDZ-200-110 does not elevate LH in humans) makes it unlikely that tumors would be induced in humans by SDZ-200-110, a calcium channel blocker. The paper also indicates that rats are a poor model for human Leydig cell tumors, partly because the Leydig cell tumor incidence in aged rats is up to 100% where as the incidence in humans is 0.0001%.

(2) Another submitted reference,
[F Neumann. Early Indicator for Carcinogenesis in Sex-Hormone-

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Sensitive Organs. Mutation Res. 248: 341-356 (1991)] presents evidence that LH stimulation in rats causes benign Leydig cell tumors. Human chronic gonadotropin (HCG), which acts like LH, induces Leydig cell tumors. In addition, when castrate rats and intact male rats are joined by parabiosis, Leydig cell tumors occur in the intact partner, presumably from the rise in LH contributed by the castrate rat. Evidently, the testosterone produced by the normal rat is not sufficient to feed back to the hypothalamus to reduce releasing hormone and thus circulating LH.

In addition, a discussion and evidence was presented on the inappropriateness of animal models for several other endocrine sensitive organs and tissues. Good evidence was presented that beagle dogs are not good models for mammary tumors in humans from long term exposure to progestogen or progestogen/estrogen combination and that rats and mice are not good models for pituitary and mammary tumors in humans from similar exposure. According to Neumann, the mammary tumors in dogs are ascribed to progestogen stimulated somatotrophic hormone (STH) release (quantified in the study). Elevated STH in dogs is known to cause pronounced mammotrophic and lactotrophic effects. In addition, symptoms of acromegaly and diabetes can be induced in dogs from progestogen stimulation. Acromegaly is induced in humans stimulated with STH, but elevated STH has never been demonstrated in women on progestogen contraceptives.

In the case of mammary, pituitary and endometrial cancer, in rats and mice, other characteristic endocrine sensitivities occur that do not occur in humans. Estrogens in rodents inhibit hypothalamic dopamine release. Dopamine inhibits prolactin release. Prolactin is released when dopamine is unavailable. Elevated prolactin levels result from this estrogen inhibition of dopamine release. This leads to hyperstimulation of the pituitary and eventually to pituitary adenomas. Prolactin also stimulates corpora lutea, which synthesizes progestogen. As a consequence, these hyperprolactinemic female rats are pseudo-pregnant. Thus, all three required mammotrophic hormones (estrogen, progestogen and prolactin) are present to chronically over stimulate tubulo-alveolar growth and breast tumors. In the case of endometrial cancer in pseudo-pregnant postmenopausal rats (50% of aged rats), dopamine agonist can inhibit the age related deficit of dopamine, resulting in inhibition of prolactin secretion, in luteolysis and removal of the progestogen dominance. After the removal of the progestogen, a few follicles form and result in estrogen stimulation. The estrogen stimulation causes permanent estrous and endometrial stimulation. Endometrial carcinoma can develop from this chronic stimulation of the endometrium. Prolactin in human females does not produce pseudo-pregnancy nor is it luteotrophic in humans or primates. Therefore, according to the reference, the different hormonal responses of rats and humans result in the rats being a poor model for these cancers induced by these hormonally active substances.

(3) The third reference,
[M Pavone-Macaluso, V Serretta, G Daricello, C Pavone, M Cacciatore, C Romano and N Caballo. Is There a Role for Pure Antiandrogens in the Treatment of Advanced Prostatic Cancer? Uro-Oncology: Current Trends, pages 149-157 (1990)]

presented a discussion of antiandrogens in the treatment of human prostate cancer. This reference contained discussion, but no data. The discussion of the pure antiandrogen, flutamide, 2-methyl-N-4-[4-nitro-3-(trifluoromethyl)phenyl]-propanamide, is relevant to vinclozolin. Flutamide is used to suppress androgen stimulated prostate cancer. The reference states that flutamide treatment of young adult men and older men causes a small increase in LH and testosterone. However, this rise in testosterone and LH is much less than the corresponding rise in treated rats. No Leydig cell hyperplasia has been observed in patients treated with flutamide. The paper does not state how many subjects with long term flutamide treatment have had testicular biopsies.

The data from these references, if accurate, indicate that elevated LH can cause Leydig cell tumors. Although, the data indicating that LH elevation causes the vinclozolin induced Leydig cell tumors is not unequivocal, it is substantial. Further literature search is necessary to quantify LH/FSH levels and timing necessary to induce Leydig cell tumors and further data is necessary to determine the dose level of vinclozolin necessary to elevate LH/FSH to these levels. In addition, other characteristics of vinclozolin should be evaluated, such as definitive studies on receptor binding and binding affinities relative to testosterone. However, the evidence suggests that vinclozolin treatment of rats results in hormonally induced Leydig cell tumors.

No evidence was submitted that hepatocellular carcinoma was caused by vinclozolin induced hormonal imbalance in these rats and no references have been found indicating hormonal imbalance from antiandrogens could cause liver cancer. Roberts et al., 1990, state that at 62.5 mg of SZD-200-110/kg/day no tumors other than Leydig cell tumors were induced in the 2-year rat study. However, it should be noted that in a 90-day study, vinclozolin at 4500 ppm caused increased androgens; a 276% rise in testosterone and a 189% rise in dehydroepiandrosterone. The implications of these anabolic steroids in the presence the xenobiotic, vinclozolin, on liver cancer needs further investigation. Androgen is known to induce sex specific mixed function oxidases in rat livers (Mastri and Lucier, 1985).

Mastri, C and Lucier, G. Actions of Hormonally Active Chemical in the Liver. In Endocrine Toxicology, ed. Dixon, RL. 1985, page 347, Raven Press, NY.

6(a)(2) CMEMO Effects of Vinclozolin on Chronic/423551-01, -02, Two Reversibility Studies/423551-03, & -04 and Literature/No MRID#/D179889/B:\VINCLV33.23C\CMICHRR2.6a2/DANDERSON/9/9/92* (Edited 12/8/92, 12/9/92).